Medical Staff Conference

The Adult Respiratory Distress Syndrome
New Insights Into Diagnosis, Pathophysiology, and Treatment

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, and John G. Fitz, MD, Assistant Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *For this Medical Staff Conference, we are pleased to have Dr Michael Matthay, Associate Professor of Medicine and Anesthesia and Associate Director of the Intensive Care Unit. He will discuss the adult respiratory distress syndrome.*

MICHAEL A. MATTHAY, MD†: The adult respiratory distress syndrome (ARDS) was first described in 1967. Although Petty and co-workers are correctly given credit for this description, a careful reading of Osler's textbook of medicine elicits an excellent description of the early phase of the syndrome. Osler wrote that "uncontrolled septicemia leads to frothy pulmonary edema that resembles serum, not the sanguinous transudative edema fluid seen in dropsy or congestive heart failure."[2] There were no mechanical ventilators or intensive care units in Osler's time, so he could not tell us more about ARDS because the development of this type of exudative pulmonary edema was usually a terminal complication. Since the adult respiratory distress syndrome was described more than 20 years ago, however, it has become a widely recognized, frequent cause of acute respiratory failure in patients treated both medically and surgically. In the early 1970s, the National Institute of Health began to invest heavily in both clinical and basic research to determine the epidemiology of ARDS and to identify the primary mechanisms of acute lung injury and repair with the overall goal of discovering more effective treatment.[3]

Now, 20 years later, it is time to ask, what have we learned? This question can be divided into three major issues. First, what have we learned about the diagnosis and the definition of the adult respiratory distress syndrome, and will our expanded (1988) definition of the syndrome contribute to a better understanding of its prognosis? Second, what have we learned about the pathogenesis and the pathophysiology of ARDS? Third, what is the status of current treatment, and what new treatment options are likely to be available in the future?

Expanded Definition of ARDS

First, let us examine the evolution in our definition and understanding of ARDS over the past 20 years. In 1967 Petty and colleagues described a syndrome of acute respiratory failure characterized by noncardiogenic pulmonary edema with severe hypoxemia caused by right to left intrapulmonary shunting through air spaces that were collapsed or filled with edema fluid.[1] The chest radiograph showed diffuse pulmonary infiltrates, and there was a decrease in lung compliance, meaning that the lungs required higher than normal airway pressures to inflate them. It was estimated in 1977 that there were about 150,000 cases of ARDS in the United States annually, with a mortality of at least 50% to 60%, although prospective studies had not yet been done.[3]

The original description by Petty and associates was useful but simple, and, in view of our current clinical understanding of the syndrome, the definition needs to be expanded. In the 1970s and early 1980s, a number of prospective clinical studies provided an increased recognition of the epidemiology of ARDS and the heterogeneous clinical patterns that may occur. Second, over the past five years, there has been a growing appreciation of the systemic manifestations of the disease. In particular, we have more insight regarding the contribution of multiorgan failure as a determinant of ultimate outcome. We also have a much better understanding of the clinical effects of infection on both the initial phase and the ongoing clinical course of patients with ARDS.

Recently investigators at the University of Colorado (Denver) and the University of Washington (Seattle) medical centers reported their data from prospective studies that were designed to determine the epidemiology of ARDS.[4,5] Both studies identified the sepsis syndrome and gastric aspiration as the two clinical disorders most commonly associated with ARDS (Table 1). Also, the risk of ARDS developing increased in parallel with the number of clinical disorders that occurred in the same patient. The University of Washington study examined the time course for the development of ARDS after the start of the clinical disorder. Overall, ARDS developed in 80% of the patients within 24 hours. Subsequently, a prospective study of 40 patients with sepsis was done at UCSF. In that group of patients, the time frame for ARDS developing after sepsis was less than six hours in many patients.[6] These findings had important implications. The original hope was to intervene with treatment that would attenuate acute lung injury before respiratory failure occurred. Clearly it will be more difficult to achieve

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
PEEP = positive end-expiratory pressure
UCSF = University of California, San Francisco
vWF = von Willebrand factor

this objective because the lag time between the start of the clinical disorder—that is, sepsis—and the development of acute respiratory failure is usually brief.

Another group of investigators at the University of Texas Health Science Center (Dallas) documented the importance of multiorgan failure in ARDS.[7] The associated systemic complications of ARDS were better described, including acute renal failure, gastrointestinal dysfunction, coagulation abnormalities, central nervous system dysfunction, and hepatic disease. The majority of patients with multiorgan failure had uncontrolled infection. Clinical and pathologic comparisons were possible because most patients who died had a postmortem examination. If a patient had clinical evidence of infection but the site of infection had not been identified before death, the source of infection was usually in the abdomen, providing that the patient had positive blood cultures. In contrast, when patients had negative blood cultures with clinical sepsis, the postmortem examination showed that the origin of the infection was usually in the lung.

TABLE 1.—*Incidence of the Adult Respiratory Distress Syndrome (ARDS) Following Clinical Risks*†*

Clinical Condition	Incidence of ARDS	
	Washington‡	Colorado‡
Sepsis		
Bacteremia	...	9/239 (4)
Sepsis syndrome	5/13 (38)	...
Aspiration of gastric contents	7/23 (30)	16/45 (36)
Fracture	1/12 (8)	2/38 (5)
Multiple transfusions		
10 units/24 h	...	9/197 (5)
10 units/6 h	4/17 (24)	...
Cardiopulmonary bypass	...	4/237 (2)
Burn	...	2/87 (2)
Pneumonia in ICU	...	10/84 (12)
Disseminated intravascular coagulation	...	2/9 (22)
Pulmonary contusion	5/29 (17)	...
Near drowning	2/3	...
Pancreatitis	1/1	...
Prolonged hypotension	0/1	...

ICU=intensive care unit

*These data refer to patients with only a single risk event. Not included are those with multiple risks.
†Modified from Fowler et al[4] and Pepe et al.[5]
‡Data given as number of cases in relation to the number at risk (percent).

Another important study was published subsequently by Montgomery and co-workers from the University of Washington.[8] This study showed that the early and late mortality in patients with ARDS was related primarily to sepsis. The actual cause of death in the first three days after the beginning of ARDS was respiratory failure in only 10% of the patients. In fact, although the incidence of respiratory failure as a cause of death increased to 18% in those who died after three days, most of these patients had a complicating pneumonia. Thus, uncontrolled sepsis was the leading cause of death for both early and late mortality (Table 2).

Another recent study reported that the overall survival rate was actually only 29% in a group of 129 patients with ARDS.[9] Infection was much more common in nonsurvivors, and the lung and abdomen were the most common sites of infection. In addition, these investigators found that adequate antibiotic treatment did not favorably influence survival (Table 3). Thus, even when the patients received an appropriate course of antibiotics, the outcome was still poor.

In view of our growth in understanding both the systemic and pulmonary features of ARDS, Murray, Luce, and I have proposed an expanded 1988 definition of ARDS. We hope that this will be accepted nationally as a new standard for describing ARDS,[10] and we think that it will be useful to clinicians in community hospitals, as well as valuable for prospective clinical research.

The first part of the definition is based on a semiquantitative method for scoring acute lung injury. We developed this system a few years ago when studying the patients who were at risk for the development of ARDS from sepsis.[6] We tested the hypothesis that evidence of complement activation in the plasma of patients could predict which cases of sepsis would progress to ARDS. For the study to be done properly, at least a semiquantitative scoring system for the clinical severity of acute respiratory failure was needed. The scoring is based on a four-point system. First, the oxygenation defect is quantified by the ratio of the arterial oxygen tension to the fraction of inspired oxygen. Second, the chest radiograph is scored on

TABLE 2.—*Direct Causes of Death in Patients With the Adult Respiratory Distress Syndrome (ARDS) and Control Subjects**

Irreversible Dysfunction (Direct Cause)	ARDS Group				Non-ARDS Group			
	Early Mortality (n=10)		Late Mortality (n=22)		Early Mortality (n=25)		Late Mortality (n=30)	
	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Sepsis	3	(30)	8	(36)	3	(12)	15	(50)
Cardiac	1	(10)	5†	(23)	1	(4)	1	(3)
Respiratory	1	(10)	4‡	(18)	..	(0)	2§	(7)
Central nervous system	3	(30)	4§	(18)	13	(52)	10	(33)
Hematologic status	(0)		1	(4)	3	(12)	1	(3)
Hemorrhagic shock	2	(20)	..	(0)	5	(20)	..	(0)
Hepatic	(0)		..	(0)	..	(0)	1	(3)

*From Montgomery et al.[8]
†Three patients had sepsis and respiratory dysfunction as a contributing cause, and one patient had respiratory dysfunction as an indirect cause.
‡Sepsis was present as a contributory cause in all patients.
§Sepsis was present as a contributory cause in one patient.

TABLE 3.—*Outcome Determinants in the Adult Respiratory Distress Syndrome**

Determinant	Patients, Number	Survivors, Number	Survivors, Percent
All study patients	129	37	29
Infection			
Present	108	23	21†
Absent	21	14	67
Antibiotic therapy‡			
Adequate	69	20	29§
Inadequate	13	3	23

*Adapted from Seidenfeld et al.[9]
†$P=.01$, χ^2 contingency analysis.
‡Not significant by χ^2.
§Includes patients with known site of infection only.

a four-point system. If the chest radiograph is clear, then no points are assigned. If there is interstitial edema, one point is assigned, and then increasing points are assigned up to a maximum of four for the degree of alveolar edema and the extent of lung involvement. A radiologist is not needed to grade the film. Third, respiratory system compliance can be calculated (if the patient has an endotracheal tube and is being given oxygen) by dividing the tidal volume by the plateau airway pressure minus the level of positive end-expiratory pressure (PEEP). Finally, it is important to factor in the level of PEEP for at least two reasons: PEEP affects oxygenation, and the level of PEEP required provides some indication of the severity of respiratory failure. With this four-point scoring system, we can classify acute lung injury as mild to moderate (0.1 to <2.5) and severe lung injury or overt ARDS (≥2.5). This scoring system has been very useful. In fact, in our first study of 40 patients with sepsis, we found that ARDS occurred in 20% of the patients, but 60% of the patients had mild to moderate lung injury.[6] Thus, these findings provided a more realistic view of the spectrum of the acute lung injury that occurs after sepsis.

The second part of the expanded definition specifies the clinical disorder(s) associated with ARDS. Table 1 provides a list of the most commonly associated disorders. The most lethal and most common cause of ARDS is the sepsis syndrome. It is important to specify the microbiology of the sepsis (gram-positive, gram-negative) and to indicate the anatomic source of the infection (lung, abdomen, urine, skin, intravenous catheter, and the like). Although the prognosis has not been specifically related yet to the specific source or type of bacterial infection, careful prospective studies may yet identify important differences in the prognosis of patients with the sepsis syndrome, depending on the specific infection and source. In fact, it was recently discovered that the source of sepsis has an influence on the sensitivity of plasma markers that may be useful to predict the development of ARDS. As mentioned earlier, we studied complement levels in the plasma of septic patients before the development of acute lung injury; neither C5a nor C3a plasma levels predicted the development of ARDS.[6] However, a new study of patients with sepsis has been done that examines plasma levels of von Willebrand factor (vWF) antigen, a product of endothelial cells.[11] Data have been prospectively collected from more than 70 patients. When all the patients with sepsis were examined together, the level of vWF antigen had no predictive value. When patients with nonpulmonary sepsis were analyzed, however, then the plasma level of vWF antigen had a 77% sensitivity and 90% specificity for predicting acute lung injury.

Aspiration is another clinical disorder frequently associated with ARDS. It is not adequate, however, simply to designate that a patient had gastric aspiration. One study, for example, reported the prognostic value of oxygenation data in patients who had suffered a witnessed episode of gastric aspiration.[12] The authors determined arterial blood gases on 44 patients within an hour after the witnessed aspiration. Then they calculated the ratio of arterial oxygen tension to the alveolar oxygen tension. If the ratio was 0.5 or less, then mortality was 48%; if the ratio was greater than 0.5, then mortality was 14% ($P<.05$).[12] Thus, by including the oxygenation data, we may be able to better assess the prognosis of patients with ARDS from gastric aspiration. Of course, the type of aspiration must be specified because it can include patients who have had near drowning with fresh or salt water or patients who may have inhaled or aspirated toxins.

Major trauma encompasses another large heterogeneous group of patients. The adult respiratory distress syndrome develops in some major trauma patients in association with lung contusion or within the first 24 hours of the trauma after severe hypotension, emergency surgical treatment, and multiple transfusions.[5] ARDS develops in others when they become septic a few days after trauma. In other patients, ARDS occurs following major trauma and long bone fractures from the fat embolism syndrome. The prognosis of ARDS from fat embolism is much better, however, than that of ARDS following sepsis or immediately after major trauma, hypotension, and surgical treatment.[13] Supportive treatment simply with mechanical ventilation should result in a greater than 90% survival in patients with ARDS after fat embolism.

A number of other clinical disorders may be associated with ARDS, including drug overdoses with aspirin and with heroin. These drugs may injure the lung directly. Patients who have drug overdose associated with the use of tricyclic antidepressants or barbiturates may have lung injury from the hypotension, concomitant gastric aspiration, or other factors that need to be specified. Cardiopulmonary bypass is another important cause of ARDS, though perhaps less common than in the past. In our experience at UCSF, the prognosis for ARDS following cardiopulmonary bypass is better than from other causes of acute lung injury.[14] As we use the expanded definition of ARDS, we will probably learn more about the specific causes of clinical lung injury and the relationship of the associated clinical disorder to prognosis.

Finally, the third part of the scoring system specifies the function of the nonpulmonary organs. We need to record the renal and acid-base status, any central nervous system deficits or hematologic abnormalities, and gastrointestinal and hepatic function. Cardiovascular abnormalities were overlooked in the early descriptions of ARDS. In fact, a requirement for the diagnosis of ARDS was that the patient not have cardiac disease. In a recent review of the clinical literature, however, as many as 20% of patients with acute ARDS were found to have concomitant cardiac disease.[15-17] Because patients with acute and chronic cardiac failure have a higher risk of infection, it makes sense that they may have a higher chance of ARDS developing. If we fail to specify a patient's cardiac function when ARDS is diagnosed, then interventions that are designed to treat the lung disease or the systemic manifestations of ARDS may not be effective because we are including patients with an especially poor prognosis

due to the associated cardiac disease. Mortality in patients with pulmonary embolism, for example, has been closely linked to the presence of cardiac disease.[18,19]

To provide an example of the value of this new classification system, consider the study published in 1985 by Fowler and co-workers.[20] These investigators reported that there were three variables at the beginning of ARDS that correlated with a particularly poor outcome. They found that patients with ARDS had a mortality rate greater than 80% if a patient's initial pH remained less than 7.4 (after being intubated and mechanically ventilated), if the serum bicarbonate level was less than 20 mmol per liter (20 mEq per dl), and if the initial blood urea nitrogen level was greater than 23 mmol per liter (65 mg per dl). The ARDS patients without these findings still had a 40% mortality, but clearly the patient groups were different, though both groups of patients had the diagnosis of ARDS. This is just one example of how systemic factors may influence outcome and how it may be valuable to characterize carefully a patient's clinical status to develop a reliable prognostic system. Table 4 summarizes the three major categories in the expanded definition of ARDS.

Pathophysiology and Pathogenesis

Briefly, what we have learned about the pathophysiology and pathogenesis of ARDS in the past 20 years is that we can divide ARDS clinically and pathologically into an acute phase, a subacute phase, and a chronic phase.[21] In early studies of ARDS, the exudative, protein-rich edema, usually with large numbers of neutrophils in the air spaces and interstitium of the lung, was described. Ultrastructural studies of the lungs of patients dying in the first 24 hours of the adult respiratory distress syndrome showed evidence of lung endothelial injury, presumably leading to the capillary leak and increased permeability pulmonary edema (Figure 1).[21,22]

As we know now, however, the magnitude of lung injury in the acute phase is more extensive than originally suspected. Although initially most investigators focused on injury to the endothelium, morphologic studies published by Bachofen and Weibel[21] in 1977 showed considerable epithelial injury in patients dying of ARDS (Figure 1). Protein-rich edema along with precipitated protein in the form of hyaline membranes and cellular debris is easily identified in the air

TABLE 4.—*Criteria for Expanded Definition of Acute Lung Injury*

Severity of Acute Lung Injury
Arterial oxygenation (Pao_2/Fio_2)
Chest radiograph
Static lung compliance
Level of positive end-expiratory pressure
Associated Clinical Disorder(s)
Sepsis (microbiology, anatomic site)
Aspiration (type)
Major trauma
Drug overdose
Cardiopulmonary bypass
Systemic Organ Function
Acid-base status
Renal function
Hematologic abnormalities
Hepatic function
Central nervous system function

Fio_2 = fraction of inspired oxygen, Pao_2 = partial pressure of arterial oxygen

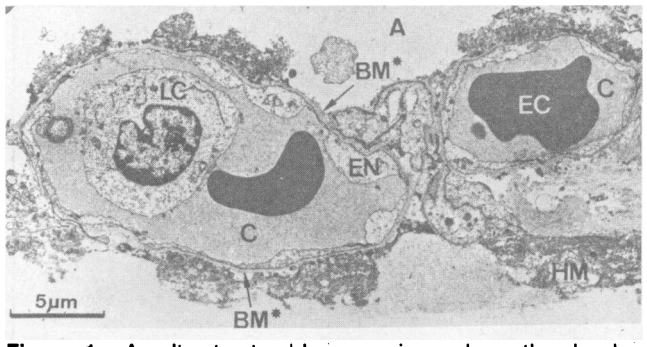

Figure 1.—An ultrastructural lung specimen shows the alveolar septum with extensive epithelial destruction in a 19-year-old woman who died after 4 days of fulminant capillary leakage due to septicemia. Note the irregularly swollen and damaged endothelium (from Bachofen and Weibel[22]). A = alveolar space, BM* = denuded basement membrane, C = capillary, EC = intravascular erythrocyte, EN = swollen endothelial cell, HM = hyaline membrane, LC = intravascular leukocyte

spaces in the acute phase of ARDS (Figure 2).[22] Epithelial injury makes sense as an important factor in outcome because the epithelium is the final barrier that guards the air spaces and allows the lung to function for its major purpose, gas exchange. The findings of a recent clinical study at UCSF suggest that the presence or absence of normal alveolar epithelial function, as measured by sequential protein concentrations in edema fluid, may be an important prognostic indicator in ARDS patients.[14]

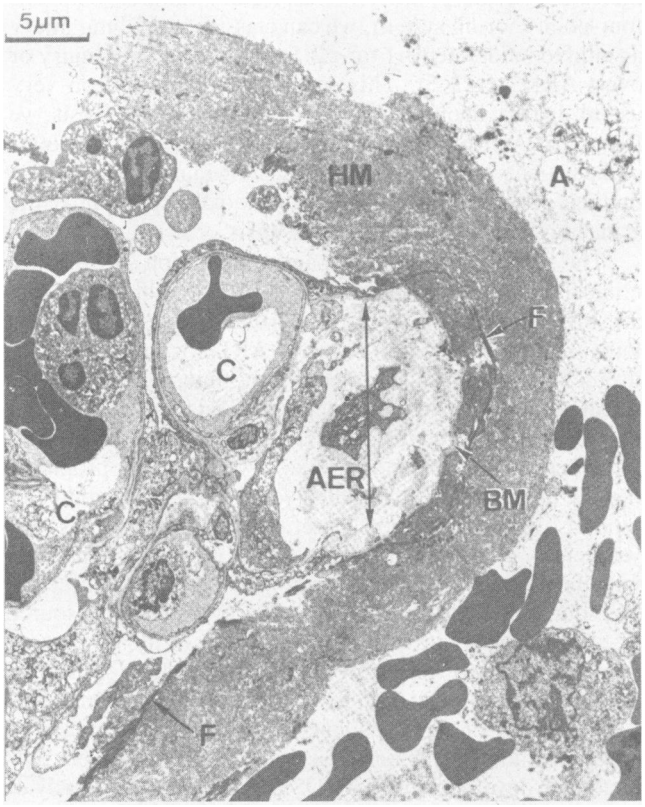

Figure 2.—An ultrastructural lung specimen from a 17-year-old woman, who died of complications that included the adult respiratory distress syndrome 3 days after a traffic accident, shows an alveolar entrance ring **(AER)** covered by a hyaline membrane **(HM)** composed of condensed plasma protein and fibrin strands **(F).** Close contact of hyaline membrane to the epithelial basement membrane **(BM)** is restricted to an area of destroyed epithelial lamina (from Bachofen and Weibel[22]). A = alveolar space, C = capillary

Originally, airway abnormalities were not identified as an important feature of ARDS. A study of survivors of ARDS showed, however, that the patients who recovered from this disease had reasonable pulmonary function, but some had reactive airway disease with no previous history of smoking and no history of asthma.[23] Subsequent clinical studies of survivors of ARDS have confirmed a significant incidence of airway disease.[24] Also, experimental studies by Snapper and associates showed that *Escherichia coli* endotoxemia caused substantial airway constriction in sheep.[25] This bronchoconstriction was mediated by thromboxane and could be inhibited by cyclooxygenase blockade with indomethacin or meclofenamate sodium. The airway constriction occurred before interstitial or alveolar edema developed in these studies. Recently, Ploysongsang and colleagues have adapted the interrupter technique to measure airway resistance in patients with ARDS and have found that at least 50% of patients with established ARDS have substantial airway abnormalities.[26]

Finally, because of the work at UCSF by Wiener-Kronish and co-workers, we now know that even the pleural space is involved in ARDS.[27,28] Originally it was thought that the absence of pleural effusions was a requirement for the diagnosis of ARDS. Because most chest radiographs of ARDS patients are taken with the patients supine, moderate-sized effusions were missed. Using two-dimensional echocardiography, Wiener-Kronish and colleagues have found that most patients with ARDS have moderately large, sterile pleural effusions.[27] On the basis of their experimental work, we know that about 20% to 25% of the excess lung water of pulmonary edema that accumulates in the acute phase drains into the pleural space and is cleared from the thoracic cavity by pleural lymphatics.[28] Thus, the pleural space is not just a passive bystander; it participates in removing a substantial fraction of the pulmonary edema fluid.

What have we learned about the subacute phase of ARDS? In this phase (five to ten days after ARDS begins), some patients have an accelerated fibrosing alveolitis. There is an impressive proliferation of alveolar type II epithelial cells that provide a new epithelial lining, apparently in response to the death of the type I alveolar epithelial cells in the acute phase. Also, there is a pronounced increase in fibroblasts and collagen formation (Figure 3). The mechanisms for these responses to the acute lung injury are poorly understood, but there is considerable interest in the presence of fibroblast and epithelial growth factors that may be released from alveolar macrophages after acute lung injury.[29] In the subacute phase, there are fewer neutrophils and more lymphocytes, plasma cells, monocytes, and cellular debris in the air spaces.[22]

Finally, in the chronic phase, which begins pathologically about 14 to 20 days after the initial insult, there is variable lung destruction with emphysema and vascular obliteration along with areas of intense fibrosis (Figure 4).[21,22]

Briefly, what are the mechanisms that may explain acute lung injury? Microthrombi and fibrin deposition are frequently found in pathologic studies of patients with ARDS, as well as in various animal models of ARDS.[30,31] Many investigators have reported an association of disseminated intravascular coagulation with ARDS.[32] One group also reported substantial elevations of a fibrin or fibrinogen degradation product, D antigen, in the plasma of patients within 60 hours after the start of ARDS.[33] Further evidence of the importance of coagulation abnormalities in the development of acute lung injury came from two experimental studies that suggested that disordered coagulation was an important etiologic factor in producing acute lung injury in animals.[34,35] Other experimental studies, however, have found that coagulation factors and platelets are not important in the initial phase of increased lung vascular permeability.[36,37]

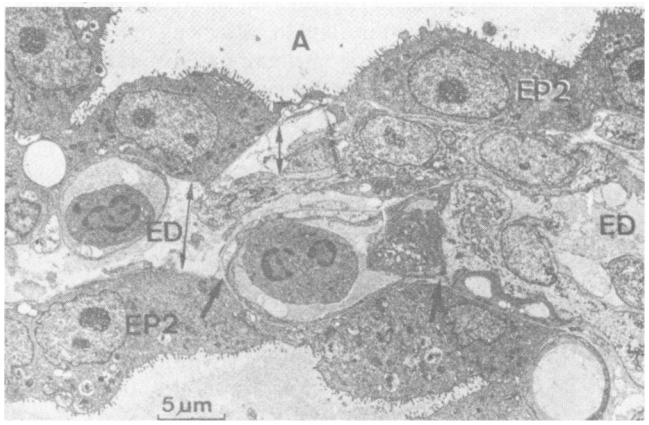

Figure 3.—An ultrastructural lung specimen from a patient about 1 week after nearly drowning shows the histologic features of the subacute stage of the adult respiratory distress syndrome. The septum is widened by interstitial edema **(ED)** fibers and cells **(double arrows)** and an almost continuous layer of bulky epithelial cells resembling type II cells **(EP2).** The single bold arrow refers to areas of fused endothelial and epithelial basement membrane. The patient had persistent sepsis from an abdominal source for 1 week (from Bachofen and Weibel[22]). A = alveolar space

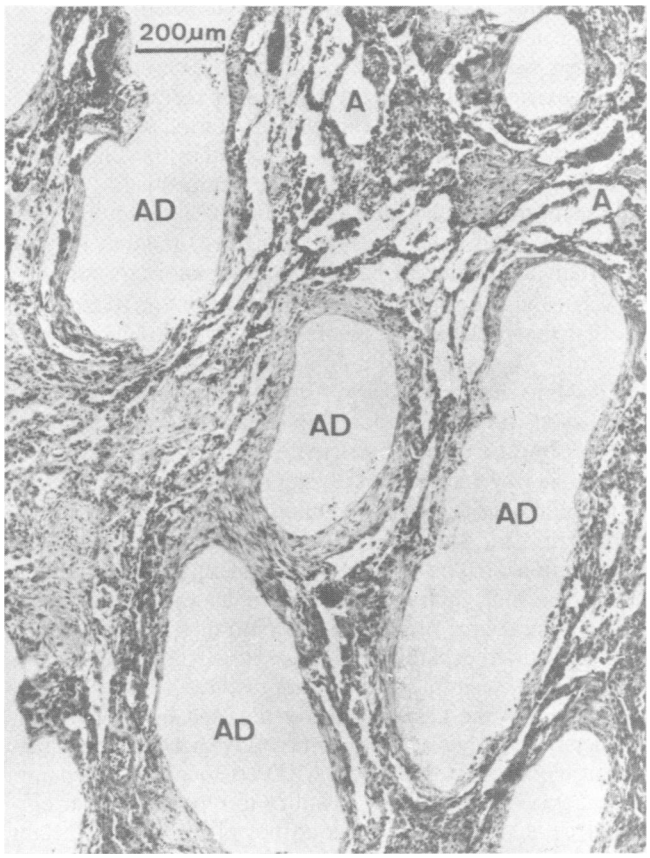

Figure 4.—Ultrastructural findings in a patient who died of progressive respiratory failure 2 weeks after abdominal septicemia began. Note there are compressed alveoli **(A)** and fibrotic tissue plates surrounding the air spaces **(AD)** (from Bachofen and Weibel[22]).

Evidence from studies in humans has implicated neutrophils in the cause of the initial lung damage in patients with ARDS. As described above, a large number of neutrophils collects in the lung in the early phase of acute lung injury.[21,38] Neutrophils also accumulate in the interstitium and air spaces of animals with experimentally induced acute lung injury.[39] Some investigators proposed that neutrophils could release toxic oxygen radicals or proteases that could then injure the endothelium and epithelial barriers in the lung.

Several experimental studies suggest that neutrophil depletion in experimental models attenuates the severity of acute lung injury.[37] In sheep given *E coli* endotoxin, the degree of lung injury was reduced if the neutrophils were first depleted with a chemotherapeutic agent like hydroxyurea. Subsequent studies have shown, however, that those studies may have been interpreted too narrowly, partly because chemotherapy affects cells other than neutrophils. The chemotherapy may have affected circulating monocytes and lymphocytes; thus, the effect may not have been related to neutrophils exclusively. In fact, one group of investigators at the University of Washington has shown that neutrophil depletion did not attenuate *E coli* endotoxin-induced lung injury in goats.[40] The role of neutrophils in the pathogenesis of ARDS remains unclear. Certainly lung injury and severe ARDS can occur without neutrophils.[41,42] The effects of neutrophils may of course also depend on injury to the endothelium that then enhances neutrophil-endothelial interactions.[43] The role of circulating monocytes both in injury and repair requires further investigation. Their role in releasing vasoactive cytokines and other factors that may amplify the inflammatory response remains to be established.

What about the resident lung cells themselves? Fifteen years ago we did not even know that intravascular macrophages existed in the lungs. Because of recent work from Warner, Brain, Staub, and other investigators, we now know that intravascular macrophages may be the first line of defense in the lung for endotoxemia or septicemia.[44,45] These cells seem to have the same properties of all macrophages. They release tumor necrosis factor in vitro, and they may be important in modulating the initial inflammatory response.

What about the damaging effects of mediators released by alveolar macrophages in the presence of acute lung injury? They may be a source of a large number of mediators that could injure the lung; however, their role has not been well established. It remains to be seen exactly whether they protect the lung or if they participate in the inflammatory response in a way that secondarily injures the lung.

What about the role of alveolar type II cells in the injury and repair after acute lung injury? I already mentioned the proliferation of type II cells in remodeling the epithelium after acute lung injury. Because alveolar epithelial type II cells are the source of surfactant, could injury to these cells contribute to the pathophysiology of ARDS? Obviously, ARDS is not as simple as the infant respiratory distress syndrome in that the latter is clearly initiated by a surfactant deficiency state. Nevertheless, one study showed that surfactant lavaged from patients with ARDS is abnormal biochemically, conceivably because of injury to type II alveolar epithelial cells.[46] Those findings do not prove that surfactant abnormalities play a major role in lung dysfunction, but they suggest that abnormalities in surfactant could play an important part in the poor lung compliance that occurs in ARDS. Finally, an area of interest to us is the possible role of type II alveolar epithelial cells in regulating alveolar liquid clearance and active ion transport. Type II alveolar epithelial cells have the capacity to transport sodium.[47,48] Studies in animals and in humans indicate that alveolar edema is cleared from the air spaces in the lung primarily by an active sodium transport system.[49,50] Type I epithelial cells may have this capacity, and type II alveolar epithelial cells certainly do. Furthermore, in studies in sheep and dogs, this ion transport system and rate of alveolar liquid clearance can be accelerated by β-adrenergic therapy.[51,52]

TABLE 5.—*Mechanisms for Injury and Repair in the Adult Respiratory Distress Syndrome*

Circulating cells	Possible mediators
Platelets	Complement system
Neutrophils	Prostaglandins
Monocytes	Oxygen radicals
? Lymphocytes	Proteases
Resident lung cells	Tumor necrosis factor
Intravascular macrophages	Other cytokines
Alveolar macrophages	
Epithelial cells, type II	
Fibroblasts	

Finally, of course, many mediators can amplify the inflammatory response (Table 5). Earlier I referred to the complement system. Although complement levels in the plasma do not predict lung injury in patients with sepsis, the role of complement in acute lung injury needs further clarification. In one recent experimental study, anti-C5a antibodies provided therapeutic benefit in a primate model of acute lung injury and the systemic manifestations of sepsis.[53] Products of both the lipoxygenase and the cyclooxygenase pathways may be involved in some of the acute responses. In a study done a few years ago, high levels of leukotriene D_4 were found in the edema fluid of ARDS patients.[54] There was a correlation between the elevated leukotriene D_4 levels and the degree of protein permeability. This finding may not indicate a cause and effect relationship but simply reflect the severity of lung injury. Oxygen radicals may be important in causing lung injury; some experimental studies have shown that agents that scavenge oxygen radicals reduce lung injury.[55] Proteases may be important in increasing the inflammatory response, but their net contribution to different types of lung injury remains to be established. Finally, the latest putative mediators include tumor necrosis factor and the interleukins. One recent experimental study indicated that the antibody to tumor necrosis factor attenuated the systemic and pulmonary effects of *E coli* sepsis in baboons if it was given two hours before the administration of live *E coli* organisms.[56]

Current and Future Therapy for ARDS

There are five categories to consider in the current and future therapy for ARDS:

- Early diagnosis, treatment, and the prevention of infection;
- Improve gas exchange;
- Limit the increased lung water;
- Increase the cardiac output and oxygen delivery because this is a systemic disease; and
- Decrease acute lung injury (Table 6).

TABLE 6.—*Current and Future Treatment of the Adult Respiratory Distress Syndrome*

Treatment Category	Therapy	
	Current	Future
Control infection	Prevention, early diagnosis, and treatment	Immunotherapy; aerosolized antibiotics
Improve gas exchange, reduce barotrauma	Positive end-expiratory pressure	Improved ventilatory modes; surfactant therapy
Limit or decrease pulmonary edema	Diuretics, maintain at lowest wedge pressure	β-Adrenergic agonists
Improve tissue oxygen delivery	Increase volume, vasopressors	Vasodilators
Attenuate pulmonary or systemic injury	Decrease Fio_2	Extracorporeal membrane oxygenation (venovenous bypass); oxygen radical scavengers; anti-tumor-necrosis-factor antibodies

Fio_2=fraction of inspired oxygen

The first and foremost issue is the early diagnosis, treatment, and prevention of infection. We have already reviewed the importance of sepsis as a cause of ARDS and as a major factor in patients' ultimate outcomes. We obviously need to reduce nosocomial infections (hand washing, remove unnecessary catheters) and also to search for surgically treatable infections. If there is a positive blood culture and an unknown source, a surgical exploration of the abdomen is frequently helpful.[7] Some investigators have suggested that there should be a trial of prophylactic aerosolized antibiotics. This proposal is based on seven-day studies in baboons in which there was a decreased incidence of secondary pneumonia with aerosolized antibiotic therapy after acute lung injury was produced experimentally.[57] Perhaps the most promising new therapeutic option for preventing and treating infection is that of immunotherapy. In a landmark study published in 1986, surgical patients who were treated with serum that was harvested from patients immunized with the J5 antibody—which is basically an extract of the endotoxin glycolipid moiety common to most gram-negative organisms—showed a notable decrease in the incidence of shock and mortality in those patients who had gram-negative infection.[58] The controls were patients with gram-positive infections for whom the J5 antibody had no effect on outcome or the incidence of shock. This type of therapy is being tested in a number of medical centers, including our own, and it may provide an important new therapy for patients with ARDS or who are at risk for ARDS.

What about treatment to improve oxygenation and minimize additional lung injury? We know that the prophylactic use of 8 cm of water of PEEP does not prevent the development of ARDS.[59] There are no data that PEEP will help resolve pulmonary edema, though the issue is controversial.[60,61] PEEP is primarily supportive therapy for improving oxygenation and allowing the fraction of inspired oxygen to be lowered. None of the newer types of ventilation—pressure control, inverse ratio ventilation, or high-frequency ventilation—have been shown to have any favorable effect on the course of ARDS, although in some circumstances pressure support ventilation may be useful to reduce the work of breathing and optimize respiratory muscle function. The best hope in this category may be with the use of surfactant. This therapy may decrease lung compliance, reduce the mean airway pressure, and perhaps allow patients to be removed from a ventilator sooner. Human trials are currently underway.

What about treatment to decrease lung edema and still maintain an adequate cardiac output? It is reasonable to maintain a patient at the lowest possible pulmonary artery wedge pressure that does not interfere with an adequate cardiac output as defined by the pH and urine flow. There are no data that prove the value of actually dehydrating a patient. In fact, because most of the edema is in the air spaces, it is unlikely that lowering the left atrial pressure makes a major difference. The best hope for reducing lung edema might be to use β-adrenergic agonist therapy that could possibly accelerate the removal of the excess liquid from the air spaces to the interstitium where the lymphatics and circulation could disperse it.[51] Further studies are needed to test this possibility.

What about cardiac function and improving tissue oxygenation? I mentioned earlier that cardiac dysfunction is not uncommon.[15–17] First, however, hypovolemia should always be considered as the most likely cause of systemic hypotension. Hypovolemia develops because of the systemic and pulmonary capillary leak as well as the PEEP-induced reduction in venous return. Therefore, modest volume expansion is the first line of therapy. Preexisting heart disease, however, is not uncommon and may require treatment with vasopressors.[16,17] Coexistent clinical illnesses, such as sepsis, may also affect cardiac function. Drug overdoses with barbiturates may decrease cardiac output. Remember that there is considerable heterogeneity among patients with ARDS in terms of their cardiac function. There is some interest in trying to increase systemic oxygen delivery, possibly with the use of vasodilators, although the net effect of this type of therapy will have to be carefully assessed.

The use of various pharmacologic agents has been proposed for their possible value in attenuating systemic and pulmonary injury. Many have been tested experimentally, and a few have been tested clinically. The clinical studies show no benefit from any pharmacologic agents so far. In particular, the effects of treatment with corticosteroids have been tested in a prospective study by Luce and colleagues here at UCSF,[62] and they have shown that corticosteroids have no benefit in patients with ARDS; other investigators have shown no benefit of using corticosteroids in cases of sepsis.[63,64] In the future, oxygen radical scavengers, anti-C5a antibodies, or anti-tumor-necrosis-factor antibodies may be of some clinical value, although experimentally they provide benefits primarily when given before sepsis occurs. There are also some recent experimental data that a monoclonal antibody to the adherence-promoting leukocyte glycoprotein, CD18, can reduce systemic organ injury and improve survival after hemorrhagic shock.[65] Finally, there has been some renewed interest in extracorporeal membrane oxygenation on the basis of an uncontrolled Italian study.[66] A controlled prospective randomized study to examine the possible value of this approach is in progress at the University of Utah.

Table 6 summarizes current and possible future therapy for ARDS. Overall, the best hope for the treatment of pa-

tients with ARDS lies with the use of immunotherapy to prevent and treat infection, surfactant therapy to improve lung mechanics and gas exchange,[67] β-adrenergic therapy to accelerate the resolution of alveolar edema,[51] and possibly monoclonal antibody therapy for leukocytic adhering glycoproteins.[65]

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